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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,551	09/27/2001	Muthiah Manoharan	ISIS-4847	3873

7590 11/20/2002

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No. 09/965,551	Applicant(s) MANOHARAN, MUTHIAH
	Examiner J. Douglas Schultz	Art Unit 1635

-- The MAILING DATE of this communication appears on th cover she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Claims 34-51 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro inhibition of ICAM transcripts, does not reasonably provide enablement for in vivo treatment or prevention of any disease associated with the undesired production of a protein, for reasons of record set forth in the Office action mailed June 5, 2002. Applicant's arguments filed September 3, 2002 have been fully considered but they are not persuasive.

Applicant's traversal of the rejection of claims 34-51 under 35 U.S.C. 112 1st paragraph enablement is based on the assertion that said rejection relied on a few select references that mischaracterize the state of the art by emphasizing the problems and failures over the successes achieved in the field. In support of this assertion, applicant provides references that demonstrate success in the use of antisense compounds in the whole animal. Applicant also argues that 35 U.S.C. 112 does not require the specification to resolve the unpredictabilities associated with the treatment and prevention of diseases as claimed. Applicant asserts that even if such a requirement existed under the law, that the specification enables the skilled artisan to carry out Applicant's method of providing treatment and prevention of diseases. In support of this, Applicant points to the specification's example of the use of antisense oligonucleotides *in vitro*, which applicant asserts is a model for *in vivo* systems, and to the demonstration of *in vivo* injections of antisense compounds, which resulted in effective delivery and systemic distribution of said compounds.

These arguments are not adopted. Applicants assertion that the references provided "mischaracterize" the state of the art is unfounded. There is no evidence to indicate how or why the five review papers referenced in the Office action of May 5, 2002, and which demonstrate Applicants lack of enablement, mischaracterize the art; furthermore, Applicant has not provided any evidence that the respective authors mischaracterized the art in the first place. While Applicant's submitted references do show some of the successes seen in the field, the preponderance of evidence, as summarized in the review articles cited in the last Office action, indicates that using antisense to provide treatment or prevention of any disease is controversial and unpredictable, as indicated by Braasch in the rejection of the last Office action: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable". Thus it is not surprising that the primary references cited in detail in Applicant's arguments all reference the novelty of demonstrating the successful use of antisense *in vivo*.

The considering the state of the art as a whole as required by *in re Wands,* it is noted that Applicants' submission of articles consists mostly of primary references, each of which describe the results of only one series of experiments; such primary research articles don't presume to indicate the state of the art as a whole. In contrast, the articles submitted by the examiner are all review papers, whose function it is to distill a large volume of primary literature, such as those submitted by Applicant, and then to discuss and analyze problems, successes, trends and future directions. It is thus difficult to comprehend how the five review articles, whose function is

essentially to characterize the state of the art, were actually mischaracterizing the state of the art during their review of anti-sense mediated gene inhibition. It is not argued that there have been irregular incidences of success in using antisense *in vivo*; however, the art of using antisense compounds successfully in vivo remains highly unpredictable, as indicated by Branch in the last Office action: "As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available." When the primary literature supplied by Applicant is put in the context of the art as a whole, as has been done in the review articles cited in the previous Office action, it is clear that such primary references supplied by Applicant do not indicate that the state of the art of providing treatment and prevention of disease using antisense compounds and methods as claimed is at all predictable, and thus enabled.

Applicant also asserts that 35 U.S.C. 112 paragraph 1 does not require the specification to provide guidance in resolving known unpredictability that exists in Applicant's claimed invention. It is held that in considering the Wands factors, the requirement exists that guidance be given from either Applicant's specification or from the prior art or a combination thereof. If the prior art is not enabling, as has been previously established, then guidance must necessarily come from the specification.

Further, Applicant argues that even if such a requirement is made of the specification, that the *in vitro* example of ICAM inhibition and the *in vivo* study of the distribution of injected antisense molecules provides enablement. This view is not adopted. While Applicant asserts that the *in vitro* example is a model of *in vivo* activity, it is reiterated that the primary reasons for lack

of enablement of such treatment *in vivo* is due to problems with non-specific interactions of administered oligos with plasma and/or cellular proteins that it encounters before contacting its target, and to significant immune reactions to said administration, and finally to problems with target access itself, that is entering the cell and binding to the transcript so that inhibition occurs. The *in vitro* model does not allow for testing or resolution of these issues, and as such cannot provide proper guidance in these areas. The in vivo distribution studies suffer the same deficiencies; simply injecting the oligo and noting where it collected in the animal would not provide guidance as to whether the gene target was actually inhibited, let alone determine if treatment or prevention associated with that protein would ever be observed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
November 15, 2002

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600